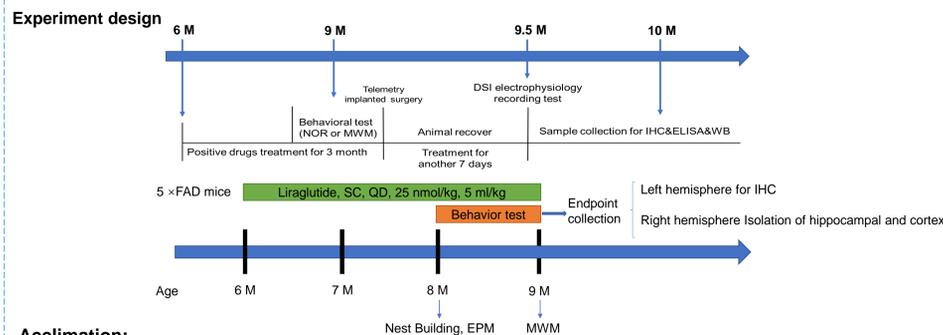


Introduction

- ◆ Evidence from clinical and molecular studies suggests that type 2 diabetes mellitus (T2DM) is associated with cognitive dysfunction, with a higher risk of developing neurocognitive disorders, including Alzheimer's disease (AD).
- ◆ Patients with type 2 diabetes exhibit elevated levels of advanced glycosylation end-product (AGEs), activating various signaling pathways through receptor for AGE (RAGE) and leading to enhanced oxidative stress and inflammation, which is a common dysregulated pathway shared by most of the comorbidities associated with AD. In addition to their revolutionary impact on diabetes and weight management, GLP-1 agonists also exhibit potential role in combating neurodegenerative conditions like AD.
- ◆ To explore the mechanisms underlying the association between AD and T2DM, we examined the therapeutic effects of the RAGE inhibitor FPS-ZM1 on cognitive function and pathology and the GLP-1 receptor agonist liraglutide on disrupted biological pathway of 5x FAD mouse model.

Methods



Acclimation:

Mice were housed in single cage for acclimation; administration was initiated after more than 7 days of adaptation.

Behavioral evaluation:

Nesting:

Mice were raised in cages by removing all stuffed toys 24 hours in advance. The nesting results were checked 12 hours after the nesting plates were placed in, and photos were taken and scored.

Elevated Plus Maze:

Mice were placed in the central area of the elevated plus maze with their heads facing the open arm end and were taken away after freely explore for 10 minutes. Their preference for open or closed arms were evaluated.

Morris water maze (MWM) Training:

Mice were given 4 trials per day for five consecutive days. They were released randomly with their heads facing the pool wall from the four compass locations, and allowed to search for the platform for 60 s. If the mouse found the platform, left it on the platform 15 s for a successful trail. If they couldn't find the hidden platform, they were guided to the platform and stayed on the platform for 15 s.

MWM Test:

After the last training trial, mice were allowed to swim in probe trial for 60s without the escape platform. Record the latency to reach the platform, the entries to platform and their time spent in target quadrant.

Electrophysiological recording:

Acute coronal brain slices were cut in 400 μm with a vibratome (VT1200S, Leica). The slices are incubated in artificial cerebral spinal fluid (ACSF) at 32°C. After 30 mins, the slices were allowed to recover for one hour at room temperature before recording. Brain slices should be transferred to the recording chamber and continuously perfused with oxygen-saturated ACSF. The field excitatory postsynaptic potentials (fEPSPs) projected from Schaffer collateral CA3 to CA1 in the hippocampus were recorded.

Sample collection:

All the animals were sacrificed after the final experiment. The brain samples were collected for IHC and WB test.

Results

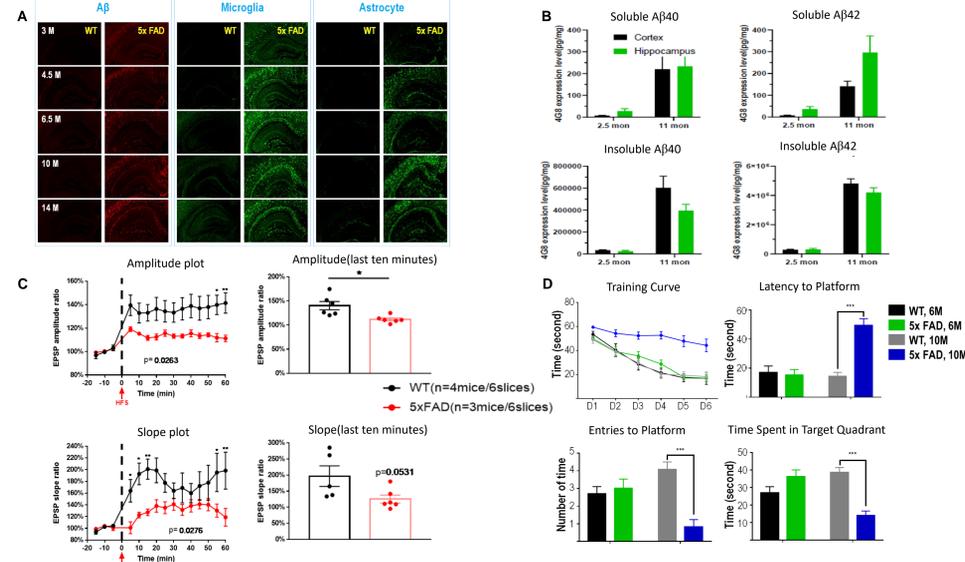


Figure 1. Pathologies Observed in 5x FAD Mice. (A-B) Pathologies of Aβ deposition, neuroinflammation and soluble/insoluble A β 42&40 increased with age. (C) LTP was impaired. (D) Impaired spatial memory was indicated by MWM.

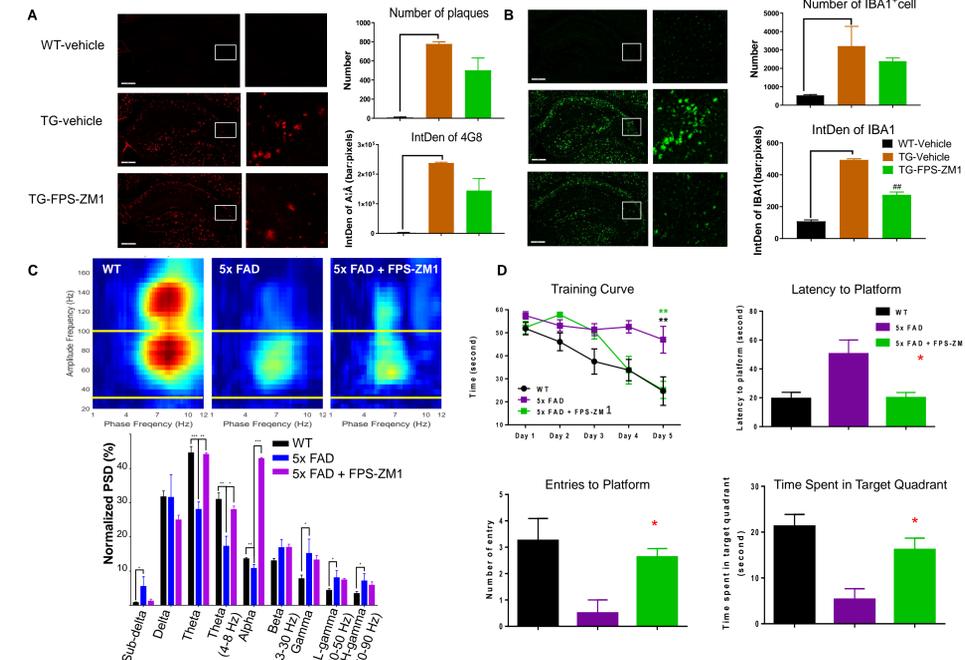


Figure 2. Efficacy Evaluation of RAGE Inhibitor FPS-ZM1 on 5x FAD Mice. (A-B) Immunostaining for 4G8 and Iba1 was performed. (C) Phase-Amplitude Coupling (PAC) was evaluated to measure neural synchronization. (D) Behavioral tests of MWM was performed to evaluate spatial memory.

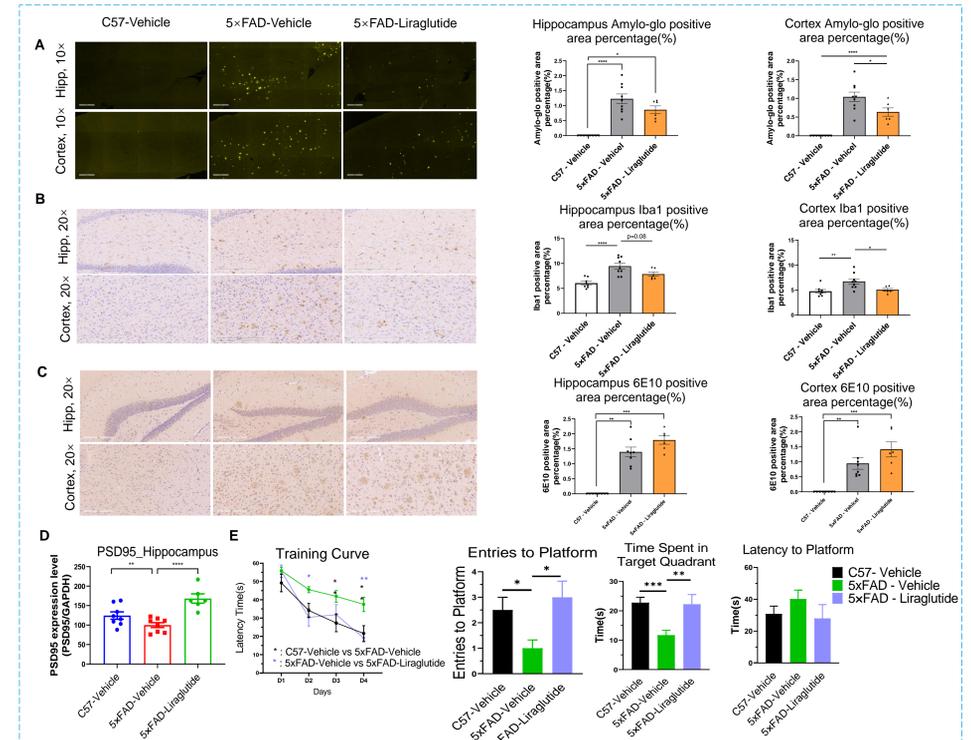


Figure 3. Efficacy Evaluation of the GLP-1 Drug Liraglutide on 5x FAD Mice. (A-C) Stainings of Amylo-glo, Iba1 and 6E10 were performed. (D) Western blotting was conducted to test Liraglutide's effect on marker proteins. (E) MWM was performed to evaluate the effect of Liraglutide.

Conclusions

- ◆ FPS-ZM1 improved the spatial learning and memory in 5x FAD mice and reduced the overall activation of microglial cell but had no effects on Aβ plaques.
- ◆ Liraglutide improved the spatial learning and memory in 5x FAD mice, reduced the level of Amylo-glo-stained Aβ plaques and the overall activation of microglial cell, improved synaptic protein levels of PSD95, but had no effect on 6E10-stained Aβ levels.
- ◆ These findings support overlapping therapeutic effects targeting RAGE and GLP-1 pathways using FPS-ZM1 and liraglutide, suggesting beneficial potentials for diabetic patients diagnosed with AD.

References

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